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(71) Applicant *(for all designated States except US)*: BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BURCHARDT, Elmar-Reinhold [DE/DE]; Dorfstrasse 28, D-58239 Schwerte (DE). MÜLLER-PEDDINGHAUS, Reiner [DE/DE]; Klutstein 22a, D-51467 Bergisch-Gladbach (DE). ABRAM, Trevor, S. [GB/GB]; 214 Marlow Bottom, Marlow, Buckinghamshire SL7 3PR (GB).

(74) Common Representative: BAYER AKTIENGESELLSCHAFT; D-51368 Leverkusen (DE).

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(54) Title: COMBINATION OF LTD, RECEPTOR ANTAGONISTS WITH GLUCOCORTICOSTEROIDS

(57) Abstract

The invention relates to a combination of glucocorticosteroids with LTD_4 receptor antagonists in medicaments for the treatment of inflammatory disorders, especially of the airways.

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Combination of LTD, receptor antagonists with glucocorticosteroids

The present invention relates to the combination of LTD_4 receptor antagonists with glucocorticosteroids (GCSs), in particular for the treatment of acute and chronic inflammatory disorders.

It is known that GCSs are used, because of their potent antiinflammatory effect, in the treatment of a large number of widely different inflammatory disorders.

GCSs modulate protein biosynthesis and are described as selective regulators of gene transcription. GCSs suppress the synthesis of cytokines and growth factors in inflammatory cells and the expression of adhesion molecules on their surface. It is likewise known that protein biosynthesis of orther gene products such as, for example, of lipocortin and of IL-6 ist induced.

Lipocortins are described as proteins regulating the activity of phospholipase A_2, which is responsible for the release of free fatty acids from phospholipid-containing membranes. Lipocortins show an antiinflammatory effect in vitro and in vivo. One of the most important free fatty acids, arachidonic acid, is metabolized by the enzymatic action of cyclooxygenases and lipoxygenases, especially 5-lipoxygenase, and converted into a variety of proinflammatory mediators.

This is why it has been assumed hitherto that the antiinflammatory effect of GCSs derives indirectly from the PLA_2-inhibitory effect of lipocortins which are induced by GCSs.

It is additionaloly known that LTD_4 receptor antagonists are used for the treatment of inflammatory, especially of allergic asthma.

On account of the mode of action hitherto described for the GCSs on eicosanoid release and the effect reported to date of the LTD_4 receptor antagonists on inflammations mediated by cysteinyl-leukotrienes, the additive effects of the combination of the two substances were completely surprising.

It has been found that the combination of LTD_4 receptor antagonists with GCSs is particularly suitable, on account of their surprising synergistic effect or for the

treatment of acute and chronic inflammatory processes, in particular for the treatment of inflammatory airway disorders such as asthma.

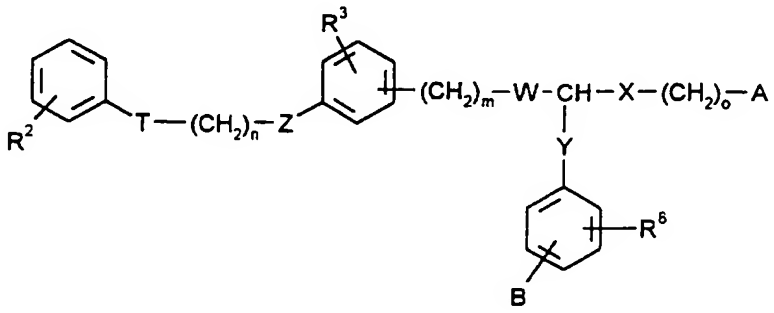
Within the scope of the invention, GCS represents the customary glucocorticosteroids such as, for example, amcinonide, beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, carbenoxolone sodium, clocortolone acetate, clocortolone pivalate, cloprednol, corticotropin (injection), corticotropin (repository), corticotropin zinc hydroxide, cortisone acetate, cortivazole, descinolone acetonide, dexamethasone, dexamethasone sodium phosphate, diflucortolone, diflucortolone pivalate, flucloronide, flumethasone, flumethasone pivalate, flunisolide, fluocinolone acetonide, fluocinomide, fluocortolone, fluocortolone caproate, fluorometholone, fluperolone acetate, fluprednisolone, fluprednisolone valerate, flurandrenolide, formocortal, fluticasone, hydrocortisone, hydrocortisone acetate, hydrocortisone buteprate, hydrocortisone butyrate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydrocortisone valerate, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium phosphate, methylprednisolone sodium succinate, nivazole, paramethasone acetate, prednicarbate, prednisolone, prednisilone acetate, prednisolone hemisuccinate, prednisoline sodium phosphate, prednisolone sodium succinate, prednisiline tebutate, prednisone, prednival, ticabesone propionate, tralonide, triamcinolone, triamcinolone acetonide, triamcinolone acetonide sodium phosphate, triamcinolone diacetate and triamcinolone hexacetonide.

GCSs which are preferably mentioned are beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, cortisone acetate, dexamethasone, dexamethasone sodium phosphate, diflucortolone, deflucortolone pivalate, flumethasone, flumethasone pivalate, hydrocortisone, hydrocortisone acetate, hydrocortisone buteprate, hydrocortisone butyrate, hydrocortisone cypionate, hydrocortisone sodium phosphate, fluticasone, hydrocortisone sodium succinate, hydrocortisone valerate, methylprednisilone, methylprednisiline acetate, methylprednisolone sodium phosphate, methylprednisolone sodium succinate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone hemisuccinate, prednisolone sodium phosphate, prednisolone

sodium succinate, prednisolone tebutate, prednisone and triamcinolone. Beclomethasone and budesonide are particilarly preferred.

LTD_4 receptor antagonists within the scope of the invention are all substances which block the biological effect of the cysteinyl-leukotrienes LTC_4 and LTD_4 at their receptor (CysLT1).

In this connection, preferred compounds are those of the gereral formula



(I)

in which

X and Y denote, identically or differently, sulphur, sulphoxide, sulphone, an alkylene chain, $-SCH_2-$ or oxygen or a direct linkage,

W denotes -CH=CH- or $-CH_2-CH_2-$,

o denotes a number from 1 to 5,

A and B denote, identically or differently, carboxyl, carboxymethyl, tetrazolyl or tetrazolylmethyl or $-CO_2R^9$ or $-CH_2CO_2R^9$ or $-CONR^{10}R^{11}$ or cyano,

n denotes a number from 1 to 10,

m denotes a number from 0 to 7,

T and Z denote, identically or differently, oxygen or a direct linkage, and

R^2, R^2, R^8 denote, identically or differently, hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro,

R^9 denotes lower alkyl and

R^{10} and R^{11} denote hydrogen, lower alkyl, alkylsulphonyl or arylsulphonyl, or they form together an alkylene chain to form a ring,

and the salts thereof.

Particularly preferred LTD_4 receptor antagonists are compounds of the formula (I) in which

X denotes sulphur, sulphone or a methylene group,

Y denotes sulphur, a methylene group, $-SCH_2-$ or a direct linkage,

W is -CH=CH-,

R^8 and R^3 denote H,

R^2 is H or F,

o is a number from 1, 2, 3 or 4,

n is a number from 2, 3, 4, 5 or 6,

m is a number from 0, 1 or 2,

T denotes oxygen or a direct linkage,

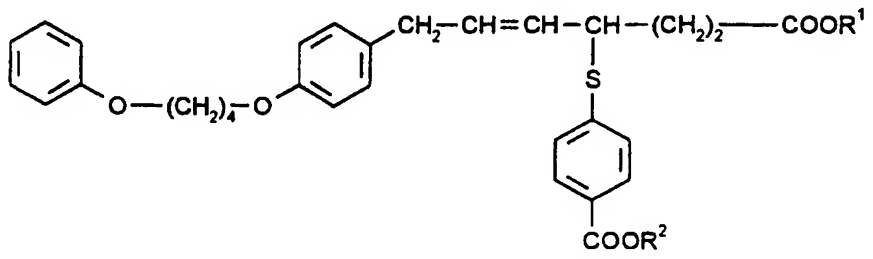
Z denotes oxygen or a direct linkage,

A denotes carboxyl or an ester thereof,

B denotes para-carboxyl or an ester thereof,

and the salts thereof.

Very particularly preferred LTD_4 receptor antagonists are those of the formula (Ia)



(Ia)

in which

R^1 and R^2 are identical or different and

represent hydrogen, a branched or straight-chain C_{1-6}-alkyl or a benzyl radical, appropriate isomers thereof, and salts thereof.

In view of the effect of GCSs an eicosanoid release and the effects of LTD_4 receptor antagonists on inflammation reaction mediated by cysteinylleukotriene, it is completely surprising to find a superadditive effect of the combinations according to the invention.

The compound of the formula (I), the processes for preparing it are descirbed in the publications EP 494 621 and Bioorg. Med. Chem. Lett. (1993), 3(8), 1517-22.

The combination according to the invention of glucocorticosteroids with the LTD_4 receptor antagonists can be used, on account of its specific properties, for the treatment of acute, chronic, autoimmune or non-autoimmune inflammations.

The combination according to the invention furthermore opens up the possibility of a significant reduction in the effective dose of the glucocorticosteroids. This makes it possible to achieve a reduction in the dosedependent unwanted effects of the medicament.

GCS and LTD_4 receptor antagonists in the combination can be combined in one or second ratio depending on the action potency of the individual substances.

The combination according to the invention can be used both in human medicine and in veterinary medicine.

Suitable indications are the treatment and prevention of inflammatory disorders of the airwagy such as allergies/asthma, bronchitis, emphysema, shock lung, pulmonary hypertension, and of the liver, intestine, kidney, pancreas, heart, nose, mouth, ears, eyes, central nervous system, muscles, connective tissue and joints, inflammations/rheumatism and oedemas, thromboses and thromboembolisms, ischaemias (disturbances of peripheral, cardiac and cerebral blood flow), infarcts (myocardial, cerebral, intestinal and other tissues), angina pectoris, inflammatory vascular disorders, arteriosclerosis, in tissue transplants, postoperative inflammations as well as vasodilatation, vessel transplant, dermatoses such as psoriasis, inflammatory dermatoses and inflammatory processes during infectious diseases (parasites, viruses, bacteria, fungi and oncoses).

The novel combination can be converted in a manner known per se, using inert, non-toxic, pharmaceutically suitable vehicles or solvents, into the customary perenteral formulations such as, for example, lyophilisates and solutions. In these, the therapeutically effective combination should in each case be present in a concentration of about 0,5 to 90 % by weight, preferably from 5 to 70 % by weight, which is sufficient to reach the stated range of dosage.

The combination can be used orally, subcutaneously, intramuscularly, intravenously or topically as aerosol (lung), ointment/cream (skin) or solution (mucous membranes).

The abovementioned pharmaceutical compositions can be produced in a conventional way by known methods, for example with the ancillary substance(s) or vehicle(s).

However, it may, where appropriate, be advantageous to deviate from the stated amounts, in particular depending on the body weight and on the mode of administration, or on the individual behaviour towards the medicament, the type of formulation thereof and the time or interval over which administration takes place. Thus, it may be sufficient in some cases to deal with less than the abovementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. When larger amounts are administered, it may be advisable to distribute these in several individual doses throughout the day.

Patent Claims

1. Combination of LTD_4 receptor antagonists with glucocorticosteroids (GCSs).

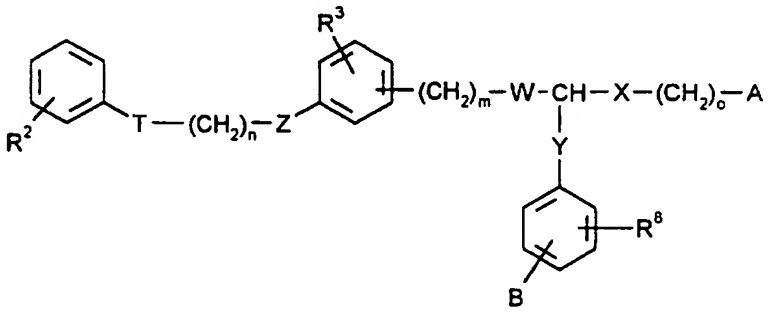
2. Combination according to Claim 1, characterized in that compounds of the group consisting of amcinonide, beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, carbenoxolone sodium, clocortolone acetate, clocortolone pivalate, cloprednol, corticotropin (injection), corticotropin (repository), corticotropin zinc hydroxide, cortisone acetate, cortivazole, descinolone acetonide, dexamethasone, dexamethasone sodium phosphate, diflucortolone, diflucortolone pivalate, flucloronide, flumethasone, flumethasone pivalate, flunisolide, fluocinolone acetonide, fluocinomide, fluocortolone, fluocortolone caproate, fluorometholone, fluperolone acetate, fluprednisolone, fluprednisolone valerate, flurandrenolide, formocortal, fluticasone, hydrocortisone, hydrocortisone acetate, hydrocortisone buteprate, hydrocortisone butyrate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydrocortisone valerate, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium phosphate, methylprednisolone sodium succinate, nivazole, paramethasone acetate, prednicarbate, prednisolone, prednisilone acetate, prednisolone hemisuccinate, prednisoline sodium phosphate, prednisolone sodium succinate, prednisiline tebutate, prednisone, prednival, ticabesone propionate, tralonide, triamcinolone, triamcinolone acetonide, triamcinolone acetonide sodium phosphate, triamcinolone diacetate and triamcinolone hexacetonide, aare empoyed as clucocorticosteroids.

3. Combination according to Claim 1, characterized in that compounds of the series consisting of beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, cortisone acetate, dexamethasone, dexamethasone sodium phosphate, diflucortolone, deflucortolone pivalate, flumethasone, flumethasone pivalate, hydrocortisone, hydrocortisone acetate, hydrocortisone buteprate,

hydrocortisone butyrate, hydrocortisone cypionate, hydrocortisone sodium phosphate, fluticasone, hydrocortisone sodium succinate, hydrocortisone valerate, methylprednisilone, methylprednisiline acetate, methylprednisolone sodium phosphate, methylprednisolone sodium succinate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone hemisuccinate, prednisolone sodium phosphate, prednisolone sodium succinate, prednisolone tebutate, prednisone and triamcinolone, are employed as glucocorticosteroids.

4. Combination according to Claim 1, characterized in that beclomethasone or budesonide are employed as glucocorticosteroids.

5. Combination according to Claim 1 to 4, characterized in that compounds of the general formula



(I)

in which

X and Y denote, identically or differently, sulphur, sulphoxide, sulphone, an alkylene chain, $-SCH_2-$ or oxygen or a direct linkage,

W denotes $-CH=CH-$ or $-CH_2-CH_2-$,

o denotes a number from 1 to 5,

A and B denote, identically or differently, carboxyl, carboxymethyl, tetrazolyl or tetrazolylmethyl or $-CO_2R^9$ or $-CH_2CO_2R^9$ or $-CONR^{10}R^{11}$ or cyano,

n denotes a number from 1 to 10,

m denotes a number from 0 to 7,

T and Z denote, identically or differently, oxygen or a direct linkage, and

R^2, R^2, R^8 denote, identically or differently, hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro,

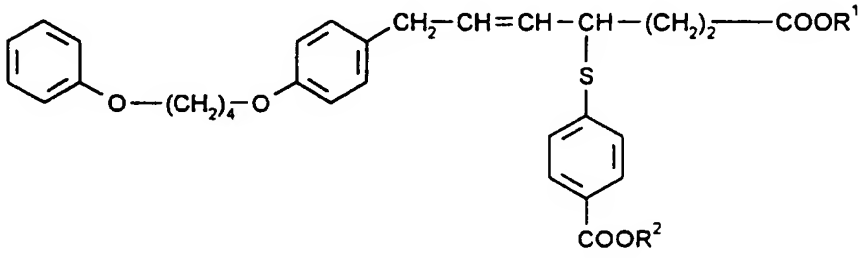
R^9 denotes lower alkyl and

R^{10} and R^{11} denote hydrogen, lower alkyl, alkylsulphonyl or arylsulphonyl, or they form together an alkylene chain to form a ring,

and the salts thereof,

are employed as LTD_4 receptor antagonists.

6. Combination according to Claim 1 to 4, characterized in that a compound of the formula



(Ia)

in which

R^1 and R^2 are identical or different,

is employed as LTD_4 receptor antagonist.

7. Combination according to Claim 1 to 6, characterized in that the ratio of glucocorticosteroid to LTD_4 receptor antagonist can be combined in another ratio depending on the action potency of the individual substances.

8. Medicament containing the combinations according to Claim 1 to 7.

9. Use of combinations according to Claims 1 to 7 for producing medicaments.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 96/04391

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/19 A61K31/235 A61K31/57 //(A61K31/57,31:235,31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 350 760 (LABELLE MARK ET AL) 27 September 1994 *cf. abstract, col. 16, lines 19-29* ---	1-9
X	US,A,5 360 815 (FORTIN REJEAN ET AL) 1 November 1994 *cf. abstract, col. 13, lines 39-49* ---	1-9
A	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 8, 1993, GREAT BRITAIN, pages 1517-1522, XP000650307 T.S. ABRAHAM ET AL.: "A new structural analogue antagonist of peptido-leukotrienes. The discovery of BAYX7195" cited in the application *cf. abstract* --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 January 1997	11.02.97

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 96/04391

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CURRENT OPINION IN INVESTIGATIONAL DRUGS (EXPERT OPIN. INVEST. DRUGS), vol. 3, no. 2, February 1994, ABOTT LABORATORIES, ABOTT PARK, ILLINOIS USA, pages 185-190, XP000610416 D.W. BROOKS: "Progress with investigational drugs for the treatment of pulmonary and inflammatory diseases" *cf. introduction and summary* ---	1-9
A	PROSTAGLANDINS, vol. 50, no. 5-6, 1995, AVENUE OF THE AMERICAS, NEW YORK, pages 269-285, XP000611799 H. TANAKA ET AL.: "The effect of a novel leukotriene C4/D4 antagonist, BAYx7195, on experimental allergic reactions" * introduction, discussion* -----	1-9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 96/04391

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5350760	27-09-94	AU-A-	7379794	28-02-95
		CA-A-	2168668	16-02-95
		WO-A-	9504741	16-02-95
		EP-A-	0712407	22-05-96
US-A-5360815	01-11-94	CA-A-	2125830	24-12-94